

Peer Review Comment Form: Guidelines for Examining Unusual Patterns of Cancer and Environmental Concerns

Consolidated Reviewer Comments and Responses

Guide to Reviewers:

The objective of peer review conducted by the Office of Science, NCEH/ATSDR, is to ensure the highest quality of science for NCEH/ATSDR guidelines, studies, and results of research. We ask that you conduct your review with this goal in mind.

Please review the guidelines provided and complete the Questions for Peer Reviewers and Recommendation sections (below). In addition, you may provide line-specific comments on the document, if you wish to do so. Please note that your unaltered comments will be shared with the program for their responses.

Please return this completed Comment Form and a track changes version (if specific comments have also been provided on the document itself) to NCEH/ATSDR via email by the agreed upon due date. Thank you for your contribution to our NCEH/ATSDR scientific efforts.

Questions for Peer Reviewers

1. Please comment on the enhanced approach for evaluating patterns of cancer routinely.

Reviewer 1: I found the enhanced approach outline for evaluating cancer patterns to be helpful and sensible. I like the flowchart but have some (minor) suggestions for improvement detailed below.

Response: Thank you for your support of the enhanced approach. The text has been modified to provide additional context for the flowchart in response to your suggestion (page 7, lines 324).

Reviewer 2: I am in full support of routine cancer pattern evaluation. But I would emphasize proactive as well as routine. The routine analysis of areas of concern is an excellent way to maintain good connections with the community, but it is not a scientific approach towards actually finding potential areas of disparate rates (the Texas Sharpshooter issue at play). So the addition of proactive vs reactive routine analysis only would be appropriate.

Response: Thank you for your suggestion regarding the routine versus proactive evaluation of cancer data. The document has been revised to indicate that both approaches be considered by STLT partners. (Pages and lines where edits were made can be added: page 7, lines 317-322; page 9, line 371 & 378)

Reviewer 3: In many ways this is one of the most important shifts in the new guidelines; it is the responsibility of STLT health departments to monitor the health of their constituents at all times, not just when called upon to “respond” to a concern. The explicit placement of these guidelines in the context of routine surveillance (for example, in Figure 1) is a notable step forward.

Response: Thank you for your support of this revision to the guidelines.

2. Please comment on the recommendations for enhancing communications and engagement with communities.

Reviewer 1: The recommendations for enhancing community communications and engagement are excellent. The expanded treatment of both aspects is a welcome addition to the Guidelines.

Response: Thank you for your support of the addition of this information to the Guidelines.

Reviewer 2: I know there are the supplemental materials for Risk Communication, but I appreciate the attention to community trust building. I think this can be underscored in nearly every section. The points of contact at the agency are important so that communications are clear and consistent. As a supplement, it would be beneficial to have a template Phase 2 response for users to adapt to ensure all the pieces are presented along with the caveats and education components.

Response: Thank you for the suggestion to develop a template for Phase 2 response. While helpful, developing such a template may require additional time that may not correspond with the release of the updated Guidelines. However, additional templates and resources will continue to be developed and made available on the CDC Cancer Cluster website, [Cancer Clusters | CDC](#).

Reviewer 3: The emphasis on partnerships and communication plans is welcome.

Response: Thank you for your support of this revision to the guidelines.

3. Please comment on the enhanced phased approach for responding to community inquiries.

Reviewer 1: I found the phased approach helpful, but, as with my response to question 1 above, I do offer some suggestions and clarifications in the line-specific suggestions below.

Response: Thank you for your suggestions. They have been incorporated. Details of where the changes have been made are indicated in the line-specific responses below.

Reviewer 2: I think the 3 phases are clear and distinct. I think that Phase 2 needs to be restructured—the numbers are not the actual order of duties. I appreciate the communication goals being woven in, but Phase 2 is a bit jumbled and might need the communication piece completely separate and part of final stage of Phase 2.

Response: Thank you for pointing out the need to clarify the content in Phase 2. We have revised Phase 2 to highlight the communication elements and separate points that guide the health department in terms of reviewing the criteria vs explaining to the community (page 17, lines 604-630).

Reviewer 3: The really important change here is that in Phase 2, the department is expected to explore multiple methods of framing the question rather than dismissing the community's initial concern out-of-hand because of a single non-significant p-value. If any formulation suggests a concern for human health, the department is expected pursue further inquiry.

Response: Thank you for your support of this revision to the guidelines.

4. Please comment on the new criteria for determining continued assessment of a report of an unusual pattern of cancer and addressing environmental concerns.

Reviewer 1: I like the new criteria. I feel the description of the activities associated with continued assessment would benefit from some additional specifics as outlined below.

Response: Thank you for your suggestions. They have been incorporated. Details of where the changes have been made are indicated in the line-specific responses below.

Reviewer 2: I think this is a great addition, my only worry is funding. But this is appropriate for 2 reasons: 1) to continue to monitor for potential problems (almost proactive surveillance); 2) continue to build trust and relationships in the community. I think the value of the second piece cannot be understated.

Response: Thank you for your support of this approach. Also, the document has been updated with "Important Reminder" boxes (page 9, lines 374-379; page 19, lines 685-690) throughout the different phases reminding STLT partners that CDC/ATSDR are available to provide assistance with any of the activities suggested in the phases. The document ends with a reminder that CDC/ATSDR are available to provide assistance (page 24, lines 890-891).

Reviewer 3: It has been unfortunate that the previous guidelines have resembled a list of opportunities for dismissing community concerns, implicitly casting the STLT departments' function as the enforcer of obstacles the community must clear in order to receive attention.

In the new guidelines, if any of several criteria are met—including some that are beyond the initial concerns raised by the community—then further attention is warranted. It is completely appropriate that departments should be expected to use their unique

expertise and access to data consider multiple paths forward beyond what communities are able to articulate on their own.

Response: Thank you for your support of this revision to the guidelines.

5. Please comment on the strengths of the proposed updated guidelines and provide suggestions to address weaknesses.

Reviewer 1:

The strengths of the proposed updated guidelines include:

- Clear articulation of steps involved in responding to unusual patterns reported by the community, to unusual patterns reported by researchers, and unusual patterns observed in routine surveillance by health departments.
- A focus on communication and engagement with communities for education on cancers, their risk factors, and the role of statistical assessments. That is, the report does a good job of pointing out that statistical significance is only one part of assessing reported clusters of cancer.

The (minor) weakness of the proposed guidelines include:

- In the flow chart it seems strange to have a path from “Further Evaluation”, “No” to “Routine Evaluation”, implying that a decision of no further evaluation leads to routine evaluation. This is potentially confusing. Perhaps “Routine Evaluation” could be replaced with “Routine Monitoring”?
- I suggest removing Figure 1 on page 11. While the figure provides an overview of the Guidance, not all terms and actions have been defined by page 11 so it seems to be to a better summary figure than an overview figure. The figure appears later with much more detailed description and, in my opinion, is much easier to follow.

Response: Thank you for your suggestions regarding the figures. Additional text has been added to clarify the difference and purpose of these figures. Details of where the changes have been made are indicated in the line-specific responses below.

Reviewer 2:

The improved case definition is important and good, but it lacks any acknowledgement of histology (although Ewing sarcoma is listed as an example).

Response: Thank you for your support of the updated case definition and raising the issue about histology. Histology is critical to the coding of cancer cases and is important guidance for cancer registry members. We prefer to limit the details of this process in the guidelines and defer to standardized registry procedures; however, we can provide links to those resources on our website.

Phase 2 steps are not clear— mixed up with communication piece with the inquirer.

Communication is likely on-going, but the education piece and highlights will be driven by the results of the Phase 2 analysis. As it is written, the two are a bit jumbled together.

Response: Thank you for your comments. We have revised Phase 2 to highlight the communication elements and separate points that guide the health department in terms of reviewing the criteria vs explaining to the community (page 17, lines 604-630)

The term privacy is used when it should be confidentiality. And perhaps issues with confidentiality will be highlighted in a supplemental document, but confidentiality should at least be cursorily addressed (group vs individual-level privacy, HIPPA vs public health confidentiality, local/state issues that prohibit sharing of information that need to be communicated upfront to the public). I have additional notes in the document.

Response: Thank you for raising this issue. Edits have been made to the document to further clarify the issues of privacy and confidentiality (page 9, lines 364-365, page 42, line 1474). The section header (page 9, line 360) has been revised, since it is possible that it could be misunderstood as a suggestion to provide individual data publicly, which was not the intent.

Reviewer 3: I do have some suggestions for Appendix A; please see question 7, below.

Response: Thank you for your suggestions. They have been incorporated. Details of where the changes have been made are indicated in the line-specific responses below.

6. Is the language in the updated guidance clear for both the general public and STLT public health agency staff?

Reviewer 1: I believe so. I suggest checking for definitions of all acronyms on their first use or adding a table of abbreviations.

Response: Thank you for your careful review. The document has been updated to ensure all acronyms have been defined on their first use.

Reviewer 2: The language is fairly straightforward and accessible in most places. However, there are areas where I feel there is overuse of acronyms and at least one example of where an acronym is used inconsistently. Unless the term is used frequently throughout the document, consider not using any acronyms unless they are universal.

Response: Thank you for bringing this to our attention. The following edits have been made to address this issue (page 3, line 123 SME has been replaced with "subject matter expert"; page 12, lines 525 PII has been replaced with "personally identifiable information"). Additional edits were made to clarify the inquirer and the community point of contact (page 13, line 537-542).

I found Appendix A to be solidly written and most of the document is likely to pass the "grandma" test of readability/comprehension.

Response: Thank you and appreciate the confirmation that the writing style is appropriate for a broader audience.

Reviewer 3: Yes.

Response: Thank you and appreciate the confirmation that the writing style is appropriate for a broader audience.

7. Please provide any additional comments about the document.

Reviewer 1: Thank you for the time devoted to collecting information and preparing the updated Guidance. I offer some line-specific comments below reflecting minor suggestions for clarification.

Response: Thank you for your time, careful review, and thoughtful suggestions. The document has been revised to incorporate these suggestions and edits. Additional details about the changes made are specified below for each of the line-specific comments provided.

Reviewer 2: Not sure where funding comes in to play—but it seems that many states do not currently have the capacity to move through all 3 Phases in the current climate, or maybe can only address one concern at a time. It might be useful to prioritize the Phase 2 steps (as well as reorganize so that the return/continual communication is separate from the actual, step-by-step analysis). Phase 3, of course, would require specific funding and not the role of most health departments' standard operations.

Response: Resources are an important factor. However, each of the phases described in the document are important. Therefore, instead of focusing or suggesting a prioritization of any of the phases the document has been updated with "Important Reminder" boxes (page 9, lines 374-379; page 19, lines 685-690) throughout the different phases reminding STLT partners that CDC/ATSDR are available to provide assistance with any of the activities suggested in the phases. The document ends with a reminder that CDC/ATSDR are available to provide assistance (page 24, lines 890-891).

Also, I like the name change. But I think environmental concerns are perhaps overemphasized. Environmental causes will nearly always be the main issue for folks calling with a concern, but social and behavior risk factors are often driving cancer patterns. And these need to be discussed/addressed in Phase 2 and accounted for in Phase 3 (only demographics is really highlighted and demographics are often proxy for SES).

Response: This update does focus more on environmental concerns than the 2013 Guidelines. We felt it was important to include considerations and resources that can help address environmental concerns that may constitute the underlying issues for a community. However, your point about considering other factors is important; especially if these non-environmental factors can explain an unusual pattern of cancer. The collection of other information is discussed on page 12, lines 514-519, but additional text

has been included (page 6, lines 243) along with other factors included in Phase 3 (page 22, line 809-810).

Reviewer 3: I understand that there is a need to keep things simple in a document such as this, but I wonder if the presentation of the formulae on page 30 describing the calculation of confidence intervals may require more context than the authors provide. The authors should consider presenting the following points:

- Multiple authors (Woodward, Epidemiology: Study Design and Data Analysis [2013]; Oleckno, Epidemiology: Concepts and Methods [2008]) caution against using against the formula presented when numbers of observed cases are small (say, less than 20), a frequent occurrence in settings such as this.
- While the importance of this imprecision can be difficult to assess in actual practice, it can be raised as further reason to avoid strict interpretations of statistical significance in weighing health risks faced by communities.
- “Strict” calculations based on the Chi-squared distribution are easily within the reach of STLT department professionals (see reference [5] in the bibliography of Appendix A). While this may sound intimidating, the R function `qchisq()` performs the necessary calculation within a single line of code, and the Excel function `=CHIINV()` enables its inclusion in a simple spreadsheet. In SAS, the function is written as `CINV()`.

Response: Thank you for these suggestions and references. The document has been revised to provide more detail on confidence intervals and additional ways to calculate using the Chi-squared statistic in R, SAS, and Excel (page 32, lines 1168-1171).

Recommendation

What is your overall recommendation on this document? Please select the appropriate category below:

Recommend Approval ()

Recommend Approval with Required Changes (X)

List recommended changes:

Reviewer 1:

1. Page 4, Literature Review, topic 2 (Focus Areas). “established a geospatial information systems (GIS) workgroup”. Typically GIS stands for “geographic information system” rather than “geospatial information system”. Appendix B refers to “geographic information systems” and I suggest using the same terminology here.

Response: Thank you for bringing this to our attention. The text has been updated accordingly (page 2, lines 78-79).

2. Page 4, Literature Review, Topic 3 (Reviews, Peer-Reviewed Articles), third bullet: I suggest changing "Rare events" to "Rare event" to read "Rare event and small area estimation statistical methods".

Response: Thank you for your recommendation. The text has been edited to reflect your suggestion (page 2, line 90).

3. Page 8, Request Cancer Cluster Investigations, second bullet list ("Respondents reported that inquiries were received from the following:"). I suggest noting that respondents could choose more than one type of inquiry (since the percentages add to more than 100%).

Response: Thank you for this suggestion. While this is true, we do not think the clarification adds to the interpretation of the results. For additional information, results from the survey analysis are available on the CDC Cancer Cluster website, [Cancer Clusters | CDC](#).

4. Page 9, line 3. "distance from a nuclear power to a ZIP code". Should this be "distance from a nuclear power plant to a ZIP code"? (I believe the word "plant" is missing). In addition, I believe there needs to be a closing parenthesis after "(8)".

Response: The additional text has been added to the document and the closing parenthesis added (page 7, line 291).

5. Page 9, line 12. I suggest changing "the exposure" to "the exposure measure/surrogate" here to note that the association is between the exposure surrogate and cancer, not necessarily the (true, unobserved) exposure and the cancer. This may be a subtle point but I feel it is good to note that the surrogate may not be a perfect measure of the true exposure.

Response: Thank you for your comment. In response, we have modified the text to include "exposure measure" (page 7, line 302) which does include surrogates. We also clarified the language in the discussion of the limitations of the studies (page 7, line 306).

6. Page 10, as noted above, I feel Figure 1 is a better summary of the approach (after all terms/actions have been defined) than it is an outline of the approach (here it occurs before some of the terms and concepts are defined). Perhaps move Figure 1 to the detailed descriptions of the Phases? Also, see my suggestion on replacing "Routine Evaluation" with "Routine Monitoring" above.

Response: We opted to leave this figure in here and added text about more detail being provided later in the document. Figures 1 and 2 are similar. However, Figure 1 describes the overall process whereas Figure 2 is specific to the elements associated with Phase 2. Given the different intents we prefer to include both figures. Additional text to introduce this section has been added for further clarification (page 7, lines 315-324). Also, "Routine Evaluation" has been replaced throughout the document with "Routine Monitoring" (page 2, line 20; page 7, line 315; page 8, line 343 (Figure 1); page 9, line 371, 378; page 15, line 584 (within graphic); page 16, line 600 (Figure 2)).

7. Page 13, Gather Information, 2nd bullet of item 2. "and inquirer" to "and how the inquirer".

Response: Thank you for suggesting this edit. The additional text added to the document (page 12, line 512).

8. Page 14, line -4. Has the acronym PII been defined?

Response: Thank you for identifying the need to define this acronym. The text has been revised accordingly (page 12, line 525).

9. Page 15, Item 2. The text following “Discuss why rates are generally calculated in 5- or 10-year intervals” does not seem to be related to 5- or 10-year intervals. This should be clearer or renamed.

Response: Thanks for your comment. The text for this section has been revised for clarification (page 17, lines 617-624).

10. Page 16, item 6. I suggest noting that observed differences may also be the result of different reporting practices in different regions (e.g., counties or states).

Response: Although some may differ in diagnostic practices, cancer registries practice uniform reporting across states. The main point here is that neighboring communities in other states or counties, should be assessed when applicable given that exposures may occur across geopolitical boundaries.

11. Page 19, Figure 2. Repeating my suggestion to replace “Routine Evaluation” with “Routine Monitoring”.

Response: This is a good point- we will change the text throughout to “routine monitoring” (page 2, line 20; page 7, line 315; page 8, line 343 (Figure 1); page 9, line 371, 378; page 15, line 584 (within graphic); page 16, line 600 (Figure 2).

12. Page 22, line 3. Add “to this contaminant” following “potential risk for exposure”.

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 21, line 738).

13. Page 22, line 4. I suggest updating “potential risk for exposure” to “potential risk for the exposure of concern” in line 4.

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 21, line 739).

14. Page 22, “Latency” paragraph. I suggest rewording to clarify the mesothelioma example by removing “(e.g., malignant mesothelioma, a lung tumor, is associated with asbestos exposure)” since this is not an example of latency yet. I then suggest updating the next sentence to read “For example, malignant mesothelioma, a lung tumor, is associated with asbestos exposure and the latent period between first exposure to asbestos and death from mesothelioma is often 30 years or longer (24).”

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 21, lines 767-768).

15. Page 23, line 7. “data is” to “data are”.

Response: Thank you for this edit. The text has been revised accordingly (page 22, line 790).

16. Page 24, Case-control study, lines 9-11. I suggest adding detail to the definition of the odds ratio to read: “Risk is often estimated as an odds ratio, showing the odds for a particular cancer to have occurred given a particular exposure, compared to odds of the same cancer without the exposure.”

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 23, line 846).

17. Page 24, Case-control study, lines 12-13. “to detect differences” to “to detect statistical differences”.

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 23, line 848).

18. Page 24, Cohort study, line 13. “may have had” to “may have experienced”.

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 23, line 862).

19. Page 28, paragraph 1, line 7. “using statistical tests like ratios” to “using statistical summaries such as ratios”. (The ratio itself is not the test).

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 29, line 1116).

20. Page 28, paragraph 2, lines 2-3. “within an area over time” to “within an area over time given existing knowledge of the type of cancer and the local population at risk.”

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 31, lines 1120-1121).

21. Page 28, paragraph 2, line 4. “population to the number” to “population compared to the number”.

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 31, line 1122).

22. Page 28, Adjusting for Factors, line 5. “comparing crude rates” to “comparing crude counts or rates”.

Response: Thank you for this suggestion. The text has been revised to reflect this suggestion (page 31, line 1133).

23. Page 30, Confidence Intervals, line 4. “Confidence intervals” to “Confidence intervals for the SIR”.

Response: Thank you for this suggestion. The text has been revised to reflect this edit (page 32, line 1158).

24. Page 30, line 4 from the bottom. “small case counts, proportion” to “small case counts, or the proportion”.

Response: Thank you for this suggestion. The text has been revised to reflect this edit (page 32, line 1165).

25. Page 31, Reference Population, line 3 from the end. “like socioeconomic” to “like age distribution, socioeconomic”.

Response: Thank you for this suggestion. The text has been revised to reflect this edit (page 33, line 1183).

26. Page 31, line 11 from the end of the page. “A type I error” to “The probability of a type I error”

Response: Thank you for this suggestion. The text has been revised to reflect this edit (page 33, line 1202).

27. Page 31, line 8 from the end of the page. “A type II error” to “The probability of a type II error”.

Response: Thank you for this suggestion. The text has been revised to reflect this edit (page 33, line 1205).

28. Page 32, line 10. I'm not sure the phrase "the Poisson distribution is often used for rates and counts" is necessary for the discussion of alpha values. It seems out of place here.

Response: Thank you for this suggestion. The text has been removed (page 34, line 1223).

29. Page 32, line 10 from the end of the page. After "by chance alone also increases", I suggest adding "(if alpha is 0.05, then we expect 5% of the results to be statistically significant by chance alone)."

Response: Thank you for this suggestion. The text has been revised (page 34, lines 1230-1231).

30. Page 32, line 6 from the end of the page. "size of the study population" to "number of people in the study population" (to avoid confusion with statistical size which has been discussed in the preceding paragraphs).

Response: Thank you for this suggestion. The text has been revised (page 34, line 1234).

31. Page 34, Geographic Visualization and Analysis, line 1. I suggest changing "during all stages when" to "for all stages of".

Response: Thank you for this suggestion. The text has been revised (page 40, line 1454).

32. Page 34, line 8 from the end of the page. "collected locally" to "collected as text".

Response: Thank you for this suggestion. The text has been revised (page 41, line 1467-1468).

33. Page 35, line 1. "residence of a cancer patient" to "residences of cancer patients".

Response: Thank you for this suggestion. The text has been revised (page 42, line 1476).

34. Page 36, line 6. "k-function" to "K-function" (this is usually capitalized in the literature).

Response: Thank you for this suggestion. The text has been revised (page 43, 1523).

35. Page 36, line 14. "GI*" to "Gi*" (I think Word autocapitalized the I).

Response: Thank you for this suggestion. The text has been revised (page 43, line 1531).

36. Page 38, line 1. "Multiple comparisons and reviews" to "Multiple comparisons of methods and reviews of techniques" (to avoid confusion with the statistical issue of multiple comparisons).

Response: Thank you for this suggestion. The text has been revised (page 45, line 1600).

37. Page 40. Check reference 29 for formatting of the authors name, it currently reads "Lawson A (Andrew B)".

Response: Thank you for identifying this mistake. The text has been revised (page 49, line 1782).

Reviewer 2:

- Clarify the national cancer surveillance system and distinguish between population-based data vs clinical/EHR data (pros/cons and when appropriate to use). Emphasize/encourage use of cancer registry data in Phase 2 (along with mortality).

Response: Thank you for pointing out this difference. The text has been edited to clarify the intent of using population-based cancer registry data (page 8, lines

350-351) and text has been added to address the use of EHR data (page 10, lines 417-419).

- Correct from privacy to confidentiality concerns and provide a little more detail.
Response: Thank you for raising this issue. Edits have been made to the document to further clarify the issues of privacy and confidentiality (page 9, lines 364-365, page 42, line 1474). The section header (page 9, line 360) has been revised, since it is possible that it could be misunderstood as a suggestion to provide individual data publicly, which was not the intent.
- Expand on health equity to include social determinates and other contextual risk factors. While the public will be primarily concerned about environmental concerns, this provides an opportunity to educate about other known risk factors and perhaps encourage the community to support targeted cancer control programs.
Response: The collection of other information is discussed on page 12, lines 514-519, but additional text has been included (page 5, line 243; page 6, lines 243), other factors included in Phase 3 (page 22, line 809-810).
- Ensure communication upfront includes what to expect in terms of range of results and why they may differ from reality. Understanding that migration or small numbers may make it impossible to determine an association (much less causal relationship) from the beginning will help communities accept results that are inconclusive or null. And this can lead to other cancer control programs being accepted by the same community.
Response: Establishing expectations early on is a critical component of these activities and agree that stating this directly is important. Additional text, including an "Important Reminder" on page 10 (lines 435-444) have been included to reinforce this concept (page 20, line 717; page 24, line 882).
- Restructure Phase 2 steps as mentioned above and in comments in text.
Response: Thank you for your comments. We have revised Phase 2 to highlight the communication elements and separate points that guide the health department in terms of reviewing the criteria vs explaining to the community (page 17, lines 604-630).

Reviewer 3: The authors are requested to consider the inclusion of the bullet points presented in the response to question 7 for inclusion in Appendix A. Because I understand the need of the authors to be concise, I offer these as suggestions rather than requirements.

Response: Thank you for these suggestions. The document has been revised to incorporate these suggestions and edits (page 32, lines 1168-1171).

Approval Not Recommended ()

List reasons for not recommending:

I have provided these line-specific comments to NCEH/ATSDR together with my Peer Reviewer Comment Form.